Research article

Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014

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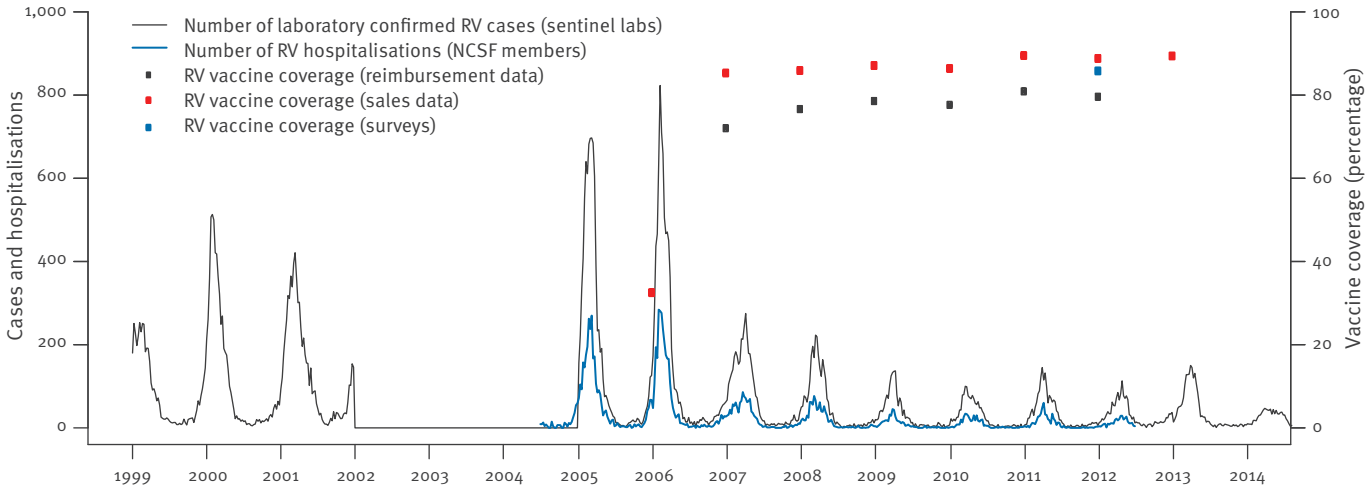
In 2006, Belgium was the first country in the European Union to recommend rotavirus vaccination in the routine infant vaccination schedule and rapidly achieved high vaccine uptake (86–89% in 2007). We used regional and national data sources up to 7 years post-vaccination to study the impact of vaccination on laboratory-confirmed rotavirus cases and rotavirus-related hospitalisations and deaths. We showed that (i) from 2007 until 2013, vaccination coverage remained at 79–88% for a complete course, (ii) in children 0–2 years, rotavirus cases decreased by 79% (95% confidence intervals (CI): 68–89%) in 2008–2014 compared to the pre-vaccination period (1999–2006) and by 50% (95% CI: 14–82%) in the age group ≥ 10 years, (iii) hospitalisations for rotavirus gastroenteritis decreased by 87% (95% CI: 84–90%) in 2008–2012 compared to the pre-vaccination period (2002–2006), (iv) median age of rotavirus cases increased from 12 months to 17 months and (v) the rotavirus seasonal peak was reduced and delayed in all post-vaccination years. The substantial decline in rotavirus gastroenteritis requiring hospitalisations and in rotavirus activity following introduction of rotavirus vaccination is sustained over time and more pronounced in the target age group, but with evidence of herd immunity.

Introduction

Globally, rotavirus is the leading cause of severe acute gastroenteritis in children aged less than 5 years, resulting in substantial morbidity and mortality [1]. Most children are infected at least once with rotavirus by the age of 5 years, with severe disease occurring most commonly between the ages of 6 months and 2 years [2,3]. Before vaccine introduction in Belgium in 2006, the burden of rotavirus disease was high compared with other European countries and rotavirus was estimated to account for nearly 5,600 hospitalisations annually in children < 7 years [4]. In June 2006, the two-dose oral monovalent vaccine (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) was marketed, followed by the three-dose oral pentavalent vaccine (RotaTeq, Sanofi Pasteur MSD, Lyon, France) in June 2007. Rotavirus vaccination has been recommended by the Superior Health Council (the Belgian National Immunization Technical Advisory Group) for all infants at 8 weeks of age since October 2006 and has been partially reimbursed since November 2006. The monovalent vaccine is administered at 8 and 12 weeks of age and the pentavalent vaccine at 8, 12 and 16 weeks of age. Since January 2007, rotavirus vaccination has been offered systematically during preventive consultations organised by the government agency well-baby clinics. All children between 0 and 3 years are actively invited via their parents or guardians to attend these easily accessible consultations in their local community, free of charge (including medical acts like prescribing and administering vaccines). Unlike other recommended childhood vaccines, rotavirus vaccines are only partially reimbursed on a per-prescription basis. Currently, EUR 11.8 per dose is co-paid by caregivers (usually the parents) of vaccine recipients [5]. Rotavirus vaccine introduction led to a substantial decline in rotavirus activity during the period from July 2007 to June 2008 [6] and a reduction

Figure 1

Weekly number of laboratory confirmed rotavirus cases and rotavirus hospitalisations in children aged 0–2 years, and annual rotavirus vaccine coverage for a complete schedule based on reimbursement data, sales data and surveys, Belgium, various seasons 1999–2014



NCSF: National Alliance of Christian Sickness Funds; RV: rotavirus.

Since October 2006, rotavirus vaccination has been recommended for all infants. Data sources are as follows: weekly number of laboratory confirmed rotavirus cases (Sentinel Laboratory Network, July 1999-June 2001 and July 2005-June 2014) and rotavirus hospitalisations (National Alliance of Christian Sickness Funds (NSCF- members), July 2004-June 2012) in children aged 0–2 years, and annual rotavirus vaccine coverage for a complete schedule based on reimbursement data (2007–2012), sales data (2006–2013) and surveys (2012).

in rotavirus-related hospitalisations in the period from June 2007 to May 2009, based on a sample of 12 hospitals in Belgium and on a study in a university hospital [7,8]. A case–control study conducted in Belgium in 2008–2010 showed that the effectiveness of two doses of the monovalent rotavirus vaccine against hospital admissions was 90% [9].

Rotavirus gastroenteritis is not mandatorily notifiable in Belgium. Surveillance is conducted through a laboratory-based sentinel network registering positive rotavirus tests, and the secondary analysis of healthcare utilisation databases (rotavirus-related hospitalisations, for which registration is obligatory). Rotavirus vaccine coverage is monitored through cluster sample surveys [10,11]. We collected all available surveillance and coverage data (one regional and seven national data sources) to study the impact of rotavirus vaccination in more detail and for a longer follow-up period. More particularly, we assessed trends in rotavirus testing and detection, hospitalisations and deaths due to rotavirus or acute gastroenteritis and rotavirus vaccination coverage. We analysed weekly rotavirus activity for up to 7 epidemiological years (1 July to 30 June) after vaccine introduction, described changes in both timing and age of rotavirus infection, obtained evidence for herd immunity, looked for changes in testing behaviour pre- and post-vaccination and estimated the coverage of the two rotavirus vaccines separately.

Methods

Data were derived from eight different databases, surveillance systems and other data sources in Belgium (Table 1). Data analysed include: vaccination coverage, number of rotavirus tests and confirmed infections, hospitalisations and deaths due to rotavirus or acute gastroenteritis. All data were processed without patient-identifying information. We assigned a random number (one, two or three tests) to weeks in which the exact number of tests/confirmed infections/hospitalisations could not be disclosed to us for privacy reasons under Belgian legislation (e.g. fewer than four tests). Analyses were performed using R [12] and SAS Enterprise Guide (version 5.1).

Vaccination coverage

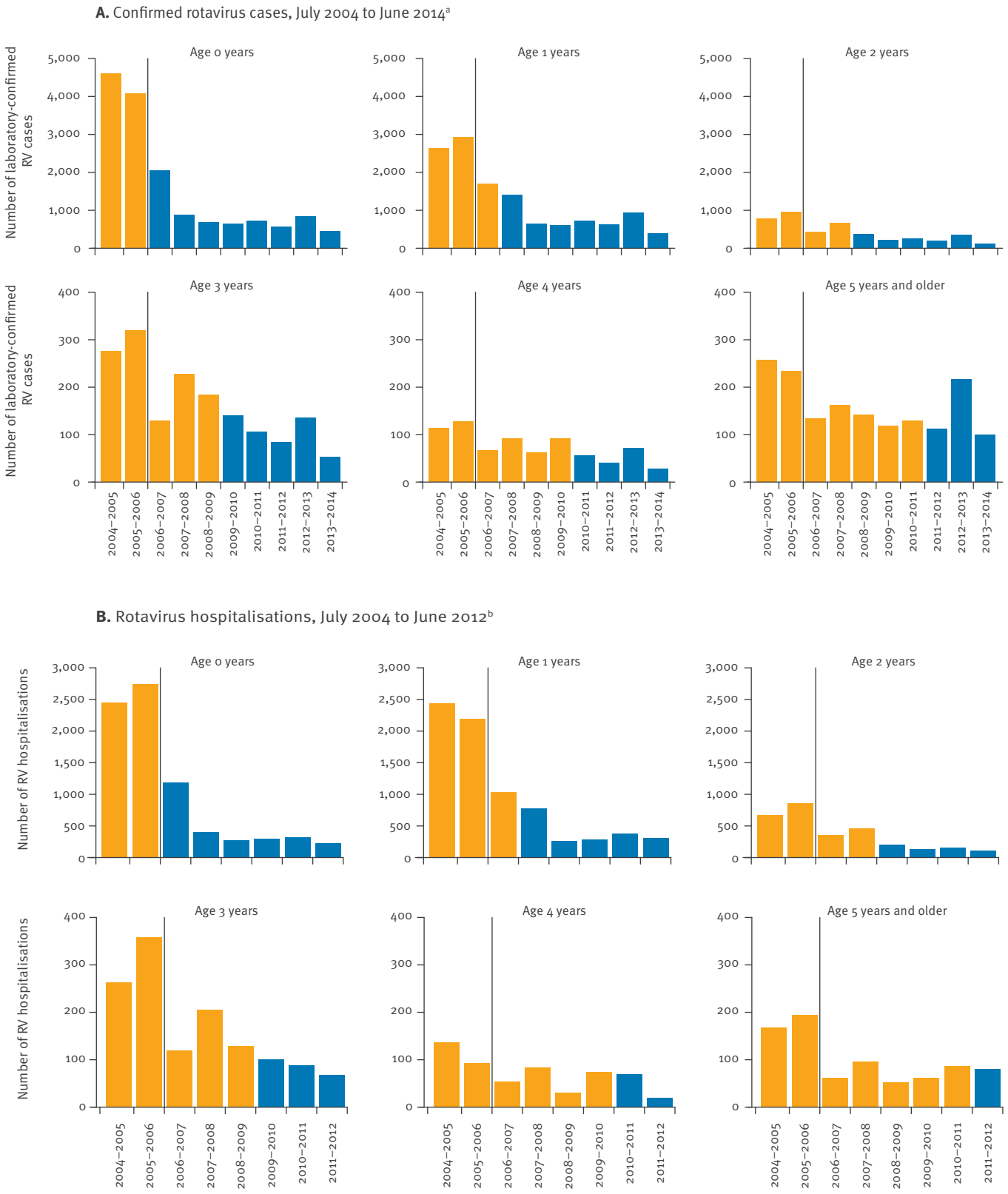
Vaccination coverage was derived from three independent sources: coverage surveys, vaccination sales data and reimbursement data.

Coverage surveys: in Belgium vaccination coverage in children is estimated in the three regions (Brussels-Capital region, Flanders and Wallonia) based on cluster sample surveys [10,11]. We estimated a national coverage for 2012 as a weighted average of the three regional rates, using the population under 1 year of age of every region of the corresponding year. Population and birth statistics were retrieved from Statistics Belgium [13].

Vaccination sales data: the annual number of doses sold in Belgium was obtained from GlaxoSmithKline Biologicals s.a (Rotarix) and Sanofi Pasteur MSD

Figure 2

Number of confirmed rotavirus cases and hospitalisations by age and rotavirus season, Belgium, various seasons, July 2004 to June 2014



RV: rotavirus.

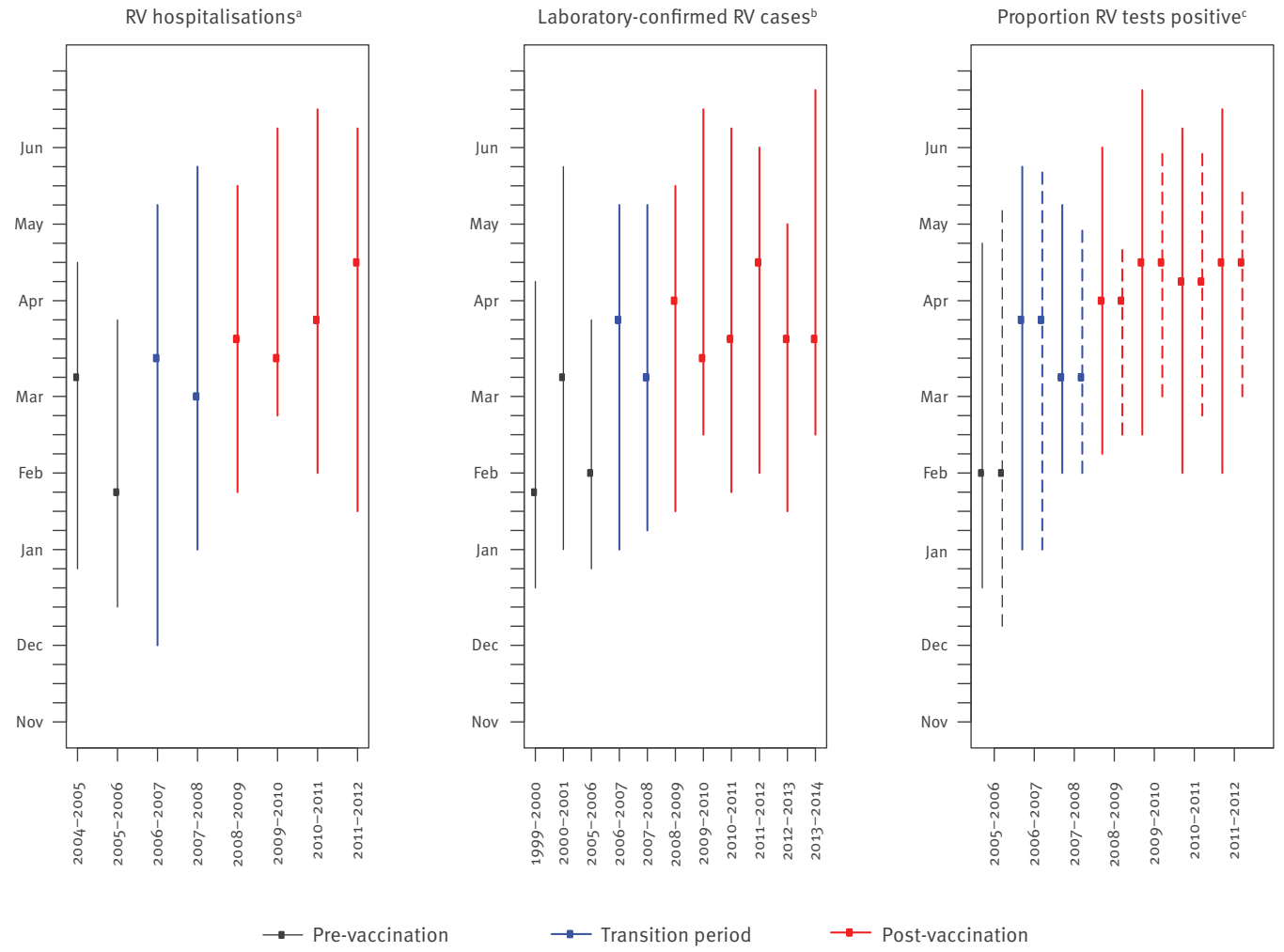
[a] Data from Sentinel Laboratory Network

[b] Data from (National Alliance of Christian Sickness Funds (NSCF- members)

Orange bars show the seasons in which a particular age group is too old to be vaccinated. For instance, in 2006–2007 children aged one year or older cannot have had a rotavirus vaccine because rotavirus vaccination has been recommended in infants only since October 2006 (vertical line). Note that the y-axes of the upper and lower row are different.

Figure 3

Rotavirus hospitalisations, rotavirus laboratory confirmed cases and proportion of rotavirus positive tests, Belgium, 1999–2014



RV: rotavirus.

[a]Data from National Alliance of Christian Sickness Funds (NSCF- members), July 2004 to June 2012.

[b]Data from Sentinel Laboratory Network, July 1999 to June 2001 and July 2005 to June 2014.

[c]Data from Inter Mutualistic Agency, July 2005 to June 2013.

For each rotavirus season, width (vertical line) and peak (point) of the rotavirus epidemic are shown.

The start/end of the epidemic for each season are defined as the week where there are more/less than the average weekly number of hospitalisations, rotavirus cases or proportion of positive tests ('method average'). For the proportion of rotavirus positive tests, the dashed lines presents the width of the rotavirus epidemic defined as the 2 first/last consecutive weeks during which the proportion of positive rotavirus tests was ≥ 10% (Tate method [22]). The peak is defined as the week with the highest number of hospitalisations, laboratory confirmed cases or proportion of positive tests.

(RotaTeq). We assumed all doses sold were administered and all infants received a complete vaccination schedule (i.e. two doses for Rotarix or three doses for RotaTeq). Annual vaccination coverage was estimated by dividing the number of complete vaccination schedules by the number of newborns in the corresponding year. Since Rotarix was put on the market on 1 June 2006, coverage for 2006 was based on the corresponding monthly birth statistics over the remaining 7 months.

Reimbursement data: the number of partially reimbursed rotavirus vaccines in Belgium was obtained from the Inter Mutualistic Agency (IMA-AIM). These

Table 1

Data sources and available time periods to determine the impact of rotavirus vaccination, Belgium, 1987–2014

Datasource	Abbreviation	Indicator	Available time period	Geographical coverage	National coverage	Pre-vaccination	Transition period	Post-vaccination
Sentinel Laboratory Network	SLN	Laboratory confirmed rotavirus infections	1999–2001 and 2005–2014	Nationwide	66.1% (average 2006–2012)	July 1999 to June 2001 and July 2005 to June 2006	July 2006 to June 2008	July 2008 to June 2014
Minimal Hospitalization Data	MHD	Hospitalisation discharge for rotavirus and all cause gastroenteritis ICD-9 (ICD-9-CM)	1999–2011	Nationwide	100%	July 1999 to June 2006	July 2006 to June 2008	July 2008 to June 2011
Carenet-National Alliance of Christian Sickness Funds	Carenet-NCSF	Health insurance data on hospital admissions for rotavirus gastroenteritis (rota or ICD-9-CM or ICD-10)	2004–2012	Nationwide	41.3% (average 2004–2012)	July 2004 to June 2006	July 2006 to June 2008	July 2008 to June 2012
Inter Mutualistic Agency	IMA-AIM	Number of reimbursed rotavirus tests and reimbursed vaccines (vaccination coverage)	2004–2012	Nationwide	100%	July 2004 to June 2006	July 2006 to June 2008	July 2008 to June 2012
Sales data	NA	Number of vaccines sold (vaccination coverage)	2006–2013	Nationwide	100%	NA	2006–2008	2008–2013
Weighted average of coverage surveys	NA	Vaccination coverage	2012	Nationwide	100%	NA	NA	2012
Standardized Procedures for Mortality Analysis	SPMA	Deaths due to gastroenteritis (ICD-9-CM or ICD-10)	1987–2000 and 2003–2010	Nationwide	100%	1987–2000 2003–2005	2006–2008	2009–2010
Cause-specific mortality Flanders	NA	Deaths due to rotavirus gastroenteritis (ICD-10)	2000–2012	Regional	54% (average 2000–2012)	2000–2005	2006–2008	2009–2012

NA: not applicable.

reimbursement data allowed us to derive the number of infants who had received at least one rotavirus vaccine dose and the number of infants who had completed a course of vaccination by week (i.e. two doses Rotarix or three doses RotaTeq). IMA-AIM data contain the delivery date of the vaccine (i.e. date of purchase), which is not necessarily the administration date. It was estimated that 70% of infants receive rotavirus vaccine within one week after purchase and 90% within 4 weeks of purchase (for all doses, unpublished data from Vaccinnet [14]). Annual vaccination coverage was calculated by dividing the number of infants with a complete vaccination scheme reimbursed, by the number of vaccine-eligible infants of the same year.

Number of rotavirus tests and laboratory-confirmed rotavirus infections

Confirmed rotavirus cases were obtained from the Sentinel Laboratory Network (SLN). The SLN is a voluntary network of microbiology laboratories that weekly reports positive results of ca 40 pathogens to the Belgian Scientific Institute of Public Health and that is representative in terms of test coverage at both the national and regional level (Flanders, Wallonia and Brussels) [15]. Rotavirus infection was included in the SLN surveillance in 1999, discontinued in 2001 and reintroduced in 2005. The discontinuation in surveillance from 2001 to 2004 was due to the withdrawal of the RotaShield vaccine (Wyeth Laboratories, Inc., PA, US) and the high workload related to case reporting for the laboratories [6]. The percentage of all rotavirus tests in Belgium covered by the SLN was stable and estimated at 66.1% (average 2006–2012; range 64.5–67.5%). For each positive test, a minimum set of epidemiological data are provided, including date of birth, sex, municipality of the case, date of detection, type of sample and laboratory technique used. No clinical or vaccination data are collected. We obtained the weekly number of positive rotavirus tests by age, as registered by the SLN for the years 1999–2001 and 2005–2014.

Table 2

Impact of vaccination on laboratory confirmed rotavirus infections and hospitalisations for acute gastroenteritis and rotavirus gastroenteritis by age strata according to different data sources used, Belgium, various seasons 1999 to 2014

Rotavirus positive tests[a] and reimbursed tests[b]										
	Pre-vaccination period		Transition period		Post-vaccination period					
	Mean rotavirus positive tests (%) July 1999 to June 2001 and July 2005 to June 2006	Mean re-imbursed rotavirus tests (%) July 2004 to June 2006	Mean rotavirus positive tests (%) July 2006 to June 2008	Mean re-imbursed rotavirus tests (%) July 2006 to June 2008	Mean rotavirus positive tests (%) July 2008 to June 2014	Mean re-imbursed rotavirus tests (%) July 2008 to June 2012	Reduction of rotavirus positive tests (%) (post/pre)	95% CI	Reduction of re-imbursed rotavirus tests of SNL (%) (post/pre)	95% CI
0–2 years[c]	6,890	47,742	3,581	40,569	1,434	32,947	79.2%	68.0–88.9	31.0%	15.6–43.0
0–11 months	3,585 (52.7%)	13,216 (27.5%)	1,408 (40.1%)	11,265 (27.8%)	592 (41.5%)	9,824 (29.8%)	83.5%	75.8–90.5	25.7%	14.2–35.6
12–23 months	2,477 (36.4%)	24,662 (51.6%)	1,559 (44.3%)	20,636 (50.9%)	601 (42.1%)	16391 (49.7%)	75.7%	61.3–87.7	33.5%	18.4–45.1
24–35 months	735 (10.8%)	9,864 (20.9%)	549 (15.6%)	8,669 (21.4%)	236 (16.5%)	6,732 (20.4%)	68.0%	39.8–85.9	31.8%	7.2–48.1
3 years and older	558	NA	405	NA	288	NA	48.5%	14.9–73.5	NA	NA
3 years	255 (45.6%)	NA	178 (44.0%)	NA	110 (38.3%)	NA	56.7%	23.0–79.8	NA	NA
4 years	102 (18.3%)	NA	79 (19.5%)	NA	54 (18.8%)	NA	47.2%	9.3–75.7	NA	NA
5-9 years	103 (18.4%)	NA	81 (19.9%)	NA	74 (25.8%)	NA	27.8%	CI includes 0	NA	NA
10 years and older	99 (17.7%)	NA	67 (16.6%)	NA	49 (17.1%)	NA	50.0%	13.9–82.1	NA	NA
5 years and older	201	NA	148	NA	124	NA	38.7%	1.4–69.2	NA	NA
Total	7,448	NA	3,985	NA	1,722	NA	76.9%	64.4–87.6	NA	NA

Hospitalisation discharge data[d]								
	Pre-vaccination July 1999 to June 2006		Transition period July 2006 to June 2008		Post-vaccination period July 2008 to June 2011			
	Mean annual number	Mean incidence rate per 100,000	Mean annual number	Mean incidence rate per 100,000	Mean annual number	Mean incidence rate per 100,000	Reduction incidence (post/pre)	95% CI
Rotavirus gastroenteritis	4,761	46.0	2,617	24.7	1,328	12.3	73.3%	70.1–75.8
Acute gastroenteritis	22,550	218.1	19,843	187.4	17,211	159.3	26.9%	22.1–31.4

Hospitalisations health insurance data[e]								
	Pre-vaccination July 2004 to June 2006		Transition period July 2006 to June 2008		Post-vaccination July 2008 to June 2012		Reduction (post/pre)	95% C)
	Mean annual number	%	Mean annual number	%	Mean annual number	%		
0-2 years	6,399		2,393		842		86.8%	84.1–89.5
0-11 months	3,038	47.5%	948	39.6%	337	40.0%	88.9%	86.2–91.5
12-23 months	2,522	39.4%	1,012	42.3%	340	40.4%	86.5%	81.9–90.3
24-35 months	839	13.1%	432	18.1%	165	19.6%	80.3	63.8–89.8
3 years and older	665		339		231		65.2%	50.2–76.1
3 years	344	51.7%	182	7.6%	105	45.5%	69.5	CI includes 0
4 years	120	18.0%	70	2.9%	51	22.1%	57.6	CI includes 0
5-9 years	161	24.2%	74	3.1%	61	26.4%	62.3	35.2–80.8
10 years and older	41	6.2%	14	0.6%	15	6.5%	63.3	CI includes 0
5 years and older	201		87		76		62.5	49.3–74.2
Total	7,064		2,732		1,074		84.8%	81.6–87.9

CI: Confidence intervals; NA: not available.

[a] Source: Sentinel Laboratory Network.

[b] Source: Inter Mutualistic Agency.

[c] In those 0-2 years the age in months was unknown in some cases.

[d] Source: Minimal Hospitalization Data.

[e] Source: Carenet-National Alliance of Christian Sickness Funds.

Reduction of disease post-vaccination is given with 95% confidence intervals.

To investigate whether a reduction in number of positive rotavirus tests was due to an actual reduction in number of rotavirus cases or merely due to changes in testing behaviour since the introduction of the rotavirus vaccines, we additionally collected the weekly number of reimbursed rotavirus tests performed by the SLN and by all laboratories in Belgium. Data were obtained from IMA-AIM, which registers all reimbursed microbiology tests per laboratory in Belgium. Rotavirus tests have been reimbursed for children ≤ 2 years of age since 1995. Weekly numbers of reimbursed rotavirus tests were obtained for the period 2004–2012. For the years 2004 and 2005 reimbursement data were only available for the 'Permanent Sample' (PS) from IMA-AIM, a representative sample which covers 2.5% of the total ensured population (in Belgium health insurance is mandatory). These data were extrapolated to the population based on the average coverage of the PS for the years 2006–2011 (for which data for both PS and the total ensured population were available). During the period 2006–2011, PS coverage did not change over time. The age of children with a reimbursed rotavirus test could not be reliably obtained from IMA-AIM, as only the year of birth is available. Therefore, the week-by-week age distribution of children < 2 years for whom tests were reimbursed was obtained from the largest health insurance company in Belgium (the National Alliance of Christian Sickness Funds (NCSF)). The NCSF covers ca 40% of all members of the ensured population included in IMA-AIM in a representative manner [16]. This age distribution was applied to the overall weekly number of reimbursed tests performed by the SLN. Data extractions and analyses related to NCSF were performed at the Medical Management Department of the NCSF under the supervision of the Chief Medical Officer.

Additionally, we calculated the weekly proportion of rotavirus tests that were positive by dividing the number of positive tests (SLN) by the number of reimbursed tests (IMA-AIM), for children ≤ 2 years of age. As children may be tested more than once for rotavirus (including multiple tests for a single episode), we identified and removed the duplicates in the SLN, IMA-AIM and NCSF databases, based on date of birth, sample week and municipality if available. Any episode occurring in the same child in the same year was considered to be a duplicate case.

Hospitalisations for rotavirus and acute gastroenteritis

Rotavirus-related hospitalisations were obtained from two independent databases.

Minimal Hospital Data

The Minimal Hospital Data (MHD) are managed by the Federal Public Service of Health and are an electronic collection of anonymised records of patients admitted to all public and private hospitals in Belgium. For the period 1999–2011, we obtained the monthly number of hospitalisations with primary discharge diagnoses of: (i) rotavirus enteritis (by diagnosis code International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 008.61) and (ii) any other acute gastroenteritis not coded as rotavirus (i.e. diarrhoea of determined aetiology (bacterial (001–005 and 008.0–008.5), parasitic (006–007) and viral (008.6)), and/or diarrhoea of undetermined aetiology (presumed infectious (008.8–009.3)) [17]. Hospitalisation rates were calculated by dividing the annual number of rotavirus enteritis or acute gastroenteritis hospitalisations by the age-specific Belgian population for the corresponding years [13]. Because the age of a hospitalised person could not be derived reliably from MHD (only year of birth is registered), the Carenet-NCSF database was used to investigate the age distribution of rotavirus-related hospitalisations (see next paragraph).

Hospital database Carenet-NCSF

Carenet is designed for electronic information exchange between hospitals and health insurance companies about hospital admissions. In July 2006 Carenet covered 88% of Belgian hospital beds, in July 2009 this increased to 99%. We could only obtain Carenet data from members of the NCSF health insurance company (see above). We obtained all records (2004–2012) on hospitalised patients who were member of the NCSF for which the diagnostic field included one of the following search strings: 'rota' or ICD-9-CM code '008.61' or ICD-10 code 'A08.0' [18]. A medical clinician searched the diagnostic fields of the retrieved records manually and selected those for which rotavirus was likely to be the main reason for hospitalisation. Data extractions and analyses related to NCSF were performed at the Medical Management Department of the NCSF under the supervision of the Chief Medical Officer.

Weekly numbers of rotavirus hospitalisations from NCSF members were used to cross-validate trends observed in MHD, to investigate the age distribution of rotavirus hospitalisations and to study a possible shift in the peak number of hospitalisations after the introduction of rotavirus vaccination.

Deaths due to gastroenteritis

We calculated the death rate in children < 5 years due to gastroenteritis using the Standardized Procedures for Mortality Analysis (SPMA) website [19]. Data were available for 1987–2000 and 2003–2010. We included all intestinal infectious diseases with ICD-9 codes 001–009. From 1998 onwards ICD-10 codes A00-A09 were used. More detailed coding of mortality data were available for Flanders for the period 2000–2012 allowing the use of ICD-10 codes (A00-A09) and the specific code for rotavirus (A08.0) [20]. The annual death rate was defined as the ratio of the number of deaths to the number of people in the age group < 5 years.

General definitions and assumptions

We defined epidemiological years from the beginning of July to the end of June of the following year. We defined three periods of analysis to reflect the introduction

of rotavirus vaccination. The pre-vaccination period includes data from July 1999 (MHD, SLN) and July 2004 (Carenet-NCSF, IMA-AIM) until June 2006 (all datasets). The transition period, during which rotavirus vaccine was first marketed and introduced, includes data from July 2006 to June 2008. The post-vaccination period includes data from July 2008 (all datasets) until June 2011 for MHD, June 2012 for Carenet-NCSF and IMA-AIM and June 2014 for the SLN (Table 1).

Currently, there is no standard way to determine the onset, peak and end of a rotavirus epidemic. Indeed, the European Centre for Disease Prevention and Control (ECDC) advises that each country specifies its own definition [21]. To explore the changes in timing and the duration of the rotavirus epidemic, we defined the start and end of the rotavirus epidemic as the week in which more or less than the average weekly number of positive rotavirus tests occurred for a particular epidemiological year ('method average'). We also used the definition proposed by Tate and colleagues ('Tate method') [22], and recommended by the ECDC when the proportion of positive rotavirus laboratory tests is available. This method defines the start and end of the epidemic for each epidemiological year as the 2 first or last consecutive weeks during which the proportion of positive tests is ≥ 10%. The peak of the epidemiological year was defined as the week with the highest number of positive rotavirus tests or rotavirus hospitalisations or proportion of rotavirus positive tests.

We estimated the vaccine impact, expressed as the percentage change, by comparing the mean number of laboratory confirmed and hospitalised rotavirus cases in unvaccinated populations (pre-vaccination period) to the mean in vaccinated populations (post-vaccination period) [23]. Confidence intervals were calculated using Fieller's method for the confidence interval of the quotient of two means, assuming Gaussian distributions [24].

Results

Vaccination coverage

Coverage surveys: national coverage in 2012 was estimated at 85.8% (95% CI: 83.0–88.2%) for a two- or three-dose schedule and 89.4% (95% CI: 87.1–91.6%) for recipients of at least one dose (Figure 1).

Vaccination sales data: in the first 7 months following vaccine introduction, vaccination coverage (two- or three-dose scheme) in infants < 1 year was 32.5% and rapidly increased to reach 89.4% in 2013, with an average of 87.5% (minimum-maximum (minmax) range: 85.5–89.4%) for 2007–2013 (Figure 1).

Reimbursement data: between 2007 and 2012, on average 85.4% (range: 80.7–88.2%) of eligible infants were vaccinated against rotavirus (88.0% (range: 80.5–99.0%) of them with Rotarix and 12.0% (min max range: 9.5–19.5%) with RotaTeq, Figure 1). Of these vaccinated infants, 9.3% did not complete the two- or three-dose scheme. This percentage slightly decreased from 10.8% in 2007 to 7.9% in 2012, and is larger for the three-dose vaccine (RotaTeq) than for the two-dose vaccine (Rotarix) (17.3% vs 6.8% in 2012). The proportion of infants vaccinated with RotaTeq (vs Rotarix) increased after its introduction up to 19.5% in 2010 and decreased thereafter, to reach 10.6% at the end of 2012.

Number of rotavirus tests and laboratory-confirmed rotavirus infections

We excluded 44,284 (24.2%) reimbursed tests from the IMA-AIM database and 2,571 (6.0%) laboratory-confirmed infections from the SLN because these were considered duplicates.

The number of laboratory-confirmed rotavirus infections in children 0–2 years of age decreased by 79.2% after widespread vaccination (Figure 1 and 2a, Table 2), whereas the number of reimbursed rotavirus tests decreased only by 31.0% (Table 2). The proportion of positive tests in the SLN decreased from 24.8% (pre-vaccination period) to 7.4% (post-vaccination period) for children 0–2 years and from 45.5% to 10.1% for infants < 1 year.

The reduction of rotavirus infections was highest in infants below 1 year of age with 80.1% (95% CI: 72.1–87.7) reduction in infants 0–5 months and 85.8% (95% CI: 78.1–92.4) reduction in infants 6–11 months of age. A substantial reduction was seen in the age groups too old to be protected directly by vaccination (i.e. evidence for herd immunity, Figure 2a). In the age group of 10 years and older, the reduction was 50.0% (Table 2).

The median age of a person tested positive for rotavirus increased from 12 months pre-vaccination to 17 months post-vaccination. In the pre-vaccination period there were more positive tests in infants 6–11 months of age (59.7%) than in 0–5 months (40.3%), while in the post-vaccination period this difference almost disappeared (51.3% in infants 6–11 months of age and 48.6% in 0–5 months). After the introduction of the rotavirus vaccination programme, a larger proportion of positive rotavirus tests occurred in children 12 months and older (Table 2). The age distribution of the number of tests reimbursed for rotavirus did not change much following widespread vaccination (Table 2).

The peak month of laboratory-confirmed rotavirus cases shifted from February in the pre-vaccination period to April after vaccination (Figure 3). The maximum weekly number of cases dropped by 77.8% (95% CI: 74.4–80.9%), from 633 cases pre-vaccination to 141 post-vaccination (Figure 1). The impact of vaccination on the duration of the rotavirus epidemics depends on the method used to determine this duration: with our approach ('method average'), no clear change was observed, but with the method used by Tate et al. [22],

post-vaccination epidemics were found to be 10 weeks shorter than pre-vaccination (Figure 3). Testing behaviour (distribution of the number of rotavirus reimbursed tests over an epidemiological year) did not change after the introduction of the vaccines (results not shown).

Hospitalisations

Based on the discharge data (MHD), the overall number of rotavirus-related hospitalisations decreased by 73.3% after widespread vaccination (Table 2). During the pre-vaccination period, the mean incidence of rotavirus hospitalisations was 46.0 per 100,000 person-years (range: 41.7–53.5), compared with 12.3 per 100,000 person-years (range: 11.7–12.9) in the post-vaccine period (Table 2). The largest reduction occurred in infants 6–11 months of age (90%, Carenet-NCSF), but a substantial reduction was also seen in persons too old to be protected directly by vaccination (Figure 2b). Before vaccination, one-third (29.2%) of children hospitalised for rotavirus were 6–11 months old. After vaccination, only one-fifth (18.3%) of rotavirus-related hospitalisations occurred in this age group. Furthermore, 43.0% of all hospitalisations occurred in infants aged 0–11 months old in the pre-vaccination period, compared with 31.4% in the post-vaccination period.

Peak number of rotavirus-related hospitalisations shifted from February to April in the post-vaccination period (Figure 3). The width of the epidemic (based on the 'method average') did not change.

The mean incidence of all-cause acute gastroenteritis hospitalisations decreased by 26.9% (95% CI: 22.1–31.4%) between the pre- and post-vaccination period (MHD, Table 2). In the pre-vaccination period, rotavirus infections occurred in 21.1% (range: 20.0–23.1%) of hospitalisations for acute gastroenteritis, in contrast to 7.7% (range: 7.1–8.2%) in the post-vaccination period.

Deaths due to gastroenteritis

In the period 1987–2005, between one and seven deaths per year occurred in children<5 years due to gastroenteritis, representing a death rate of 0.7 per 100,000 per year (range 0.2–1.1). In the post-vaccination period (2008–2010), the annual number of deaths varied between zero and three deaths per year (death rate: 0.2/100,000).

Based on the more detailed information in the region of Flanders (average population of 322,356 children<5 years), rotavirus was responsible for two deaths during 2000–2005, one death in the period 2006–2008 and no deaths during 2009–2012.

Discussion

During the 7 years following rotavirus vaccine introduction, we established that: (i) vaccine uptake remained high; (ii) the substantial decline in both rotavirus-related hospitalisations and laboratory-confirmed rotavirus persisted; (iii) rotavirus incidence peaked annually in spring instead of winter; (iv) the average age at infection and hospitalisation increased and (v) the number of laboratory-confirmed and hospitalised rotavirus cases decreased also in unvaccinated persons (evidence for herd immunity).

The estimated vaccination coverage was consistently high using different data sources. We found that on average 9.3% of Belgian infants did not complete their schedule, which is higher than the 2% found by a coverage survey conducted in Flanders [10]. However in Flanders, coverage and compliance with vaccinations are typically higher than in the other regions [10], and this Flemish survey considered two doses as fully vaccinated whereas a complete schedule with RotaTeq consists of three doses. Also, we found that the proportion of infants who completed the series was higher for the two-dose than the three-dose vaccine, similar to findings in the United States (US) [25-27].

In the pre-vaccination period, we estimate that rotavirus infections were responsible for 21.1% of hospital admissions for acute gastroenteritis, which is in line with previous European estimates (21–58% [28-30]). We found a substantial decrease in laboratory-confirmed cases and rotavirus-related hospitalisations and deaths in the post-vaccination period, which confirms the reduction of 87% of rotavirus hospitalisations predicted by a mathematical model assuming uptake rates similar to those for other routine infant vaccinations [31]. Furthermore, this considerable reduction is in line with the high effectiveness of the rotavirus vaccines (over 85%) [32]. A systematic review of ecological studies from eight countries reported a 49–89% decline in laboratory-confirmed rotavirus hospital admissions in children less than 5 years old within 2 years of vaccine introduction [33]. The evidence for a direct vaccination-related reduction is further strengthened by a lower proportion of rotavirus-positive tests in infants<1 year following rotavirus vaccine introduction, i.e. a decrease from 45.5% to 10.1%.

In addition, the typical rotavirus seasonal peak apparent in winter and early spring before introduction of the vaccine was reduced and delayed in all post-vaccination years. Although pre-vaccination this was based on data from only 3 (laboratory tests) or 2 (hospitalisations) epidemiological years, these results pointed in the same direction for both. These changes in seasonal patterns are unlikely to be due to year-to-year variations, and probably reflect a decline in virus transmission, as predicted by mathematical modelling applied to England and Wales [34]. In the Netherlands, where a rotavirus vaccination programme is absent, the peak rotavirus incidence was exceptionally low in 2013–14 [35]. The authors offered as explanations the low birth rate, mild winter, high rotavirus incidence in the previous year and the introduction of rotavirus vaccination in neighbouring countries. Also in Belgium we found the number of rotavirus positive tests in 2013–14 to be lower than in any of the

previous epidemiological years, although much less pronounced than in the Netherlands. During that epidemiological year, birth rate, vaccination coverage and rotavirus testing behaviour did not change compared with the previous epidemiological years, and no exceptionally high rotavirus peak preceded 2013–14 [13]. Besides, although 2013–14 was characterised by an exceptionally warm winter, this was also the case for 2006–07 and 2007–08 [36]. Hence, the explanations proposed for the extremely low rotavirus incidence in the Netherlands in 2013–14 seem unlikely to explain the low incidence in Belgium in the same epidemiological year. Clearly, more research is needed to get insight in the cause(s) of rotavirus annual variations, both in the presence and absence of vaccination. The impact of vaccination on the average length of the rotavirus epidemic is difficult to determine due to the lack of a standard method to measure this length. According to our calculation method, the length of the yearly rotavirus epidemic was unchanged by the introduction of the vaccines. Yet, the method described by Tate and colleagues [22] suggests a 10-week decrease. Note that comparison between the two methods is difficult as only one pre-vaccination epidemiological year was available for the proportion of rotavirus tests being positive. We did not observe clear biennial increases in rotavirus activity in the post-vaccine era as observed in the US [22]. This might be due to different transmission patterns resulting from the lower speed and level of vaccine uptake in the US vs Belgium. In the US, rotavirus vaccines have been recommended for routine use since 2006 and coverage (of mainly the three-dose vaccine) increased gradually from 44% in 2009 to 73% in 2013 for a complete schedule [37], whereas vaccination coverage in Belgium increased to 79–88% within 7 months. The free of charge, low-threshold community outreach vaccination for Belgian infants (together with using predominantly the two-dose rotavirus vaccine) could lead to higher vaccination coverage and better completion rates. Another reason could be that the two vaccines differ in strain composition and may therefore exert different pressures on the circulating serotypes and overall transmission dynamics. It remains difficult, however, to explain differences in cycling patterns: modelling studies show that small changes in rotavirus transmission dynamics can lead to very different cycling patterns [38,39].

We observed an increase in the median age of confirmed rotavirus cases. This was predicted by a model applied to England and Wales, based on vaccination coverage of 91% [34]. We did not observe an increase in hospitalisations in older children, in contrast to the findings in Austria, where during the fourth year post-vaccination an increase of 48% in hospitalisation rates for rotavirus was observed in children 5–9 years of age [40]. Such increase was also predicted by models assuming the probability of infection to depend on the number of previous infections, and not on age [38,39]. Paulke-Korinek and colleagues mention that the incidence increase in Austria could also be due to very high rotavirus activity in 2011 [40]. In Belgium, an increased rotavirus activity was noted in 2012–13 compared with the previous epidemiological year (Figure 2a), but it is not known if this is reflected in an increase in hospitalisations, since these data are not yet available.

In the age group older than 10 years, who were not yet vaccinated, we observed a 50.0% decrease in confirmed rotavirus cases, suggesting an indirect protection. In many countries, the reduction in rotavirus disease has indeed been broader than expected based on vaccine coverage alone [33]. The decrease in symptomatic infections in the vaccinated population most likely leads to a reduced chance of being exposed to infection for those not immunised [34].

The results of this descriptive and ecological design may reflect factors not related to immunisation, such as natural fluctuations or strain variation [41]. For instance, increased circulation of a specific rotavirus strain causing relatively mild disease could result in lower rotavirus related disease burden. However, after vaccine introduction in Belgium, G2P [4] strains, which are associated with more severe gastroenteritis [42,43] were observed to increase relative to other strains [44]. Also, the increased proportion of G2P [4] was seen more in vaccinated compared with unvaccinated children, suggesting strain-specific differences in vaccine effectiveness is playing a role in altering the genotype distribution [44]. Despite this strain shift, our study shows a strong decrease in various manifestations of the rotavirus disease burden, confirming rotavirus vaccination is highly effective in reducing disease.

Hospitalisation data might be inconsistent in relation to rotavirus coding based on irregular laboratory confirmation and the potential influence of rotavirus vaccination on coding practices. However, all findings were consistent using different independent data sources (including two parallel hospital databases), with different methods of registering diagnoses. Moreover, the proportion of positive tests decreased, reflecting lower rotavirus prevalence and we found no evidence of important changes in testing behaviour based on the number and the seasonal distribution of reimbursed tests. However, the reductions in rotavirus burden calculated using different data sources should be compared with caution, as the different data sources did not cover the same periods. Nevertheless, epidemiological years 2005 to 2010 were covered by all data sources, and the results pointed clearly in the same direction. We took a conservative approach in identifying duplicates, assuming a maximum of one episode per year. This implies an underestimation of rotavirus burden as a second infection occurred in 4% of Mexican infants by 6 months of age and nearly 30% by 1 year of age [45]. However, because the probability to be symptomatic decreases with increasing number of previous infections [45,46] and because recurrent infections occurred at a slower pace [46], we believe

with our conservative approach we have not missed many episodes.

Conclusion

Rotavirus vaccination had a substantial and sustained public health impact up to 7 epidemiological years after vaccine introduction, most pronounced in the target age group but with evidence of herd immunity in unvaccinated age groups.

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Conflict of interest

None

Authors' contributions

MS and JB contributed to the conception and design of the study, the data collection and analysis and drafting of the article. NB contributed to the data collection and took part in drafting the article. AB contributed to the data collection and analysis. BO contributed to the data collection. MC contributed to the data collection and analysis. PVD, PB, KVH and TG contributed to the interpretation of data and critically appraised the drafts. All authors were involved in revising the manuscript and read and approved the final manuscript.

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